Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

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Paragraph 2.3

Remarkable effects of imatinib in a family with young onset gastrointestinal stromal tumors and cutaneous hyperpigmentation associated with a germline *KIT*-Trp557Arg mutation: case report and literature overview

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Abstract

Gastrointestinal stromal tumors (GISTs) occur mostly sporadically. GISTs associated with a familial syndrome are very rare and are mostly wild type for *KIT* and platelet-derived growth factor alpha (*PDGFRA*). To date 35 kindreds and 8 individuals have been described with GISTs associated with germline KIT mutations. This is the third family described with a germline p.Trp557Arg mutation in exon 11 of the *KIT* gene. The effect of imatinib in patients harboring a germline KIT mutation has been rarely described. Moreover, in some studies imatinib treatment was withheld considering the lack of evidence for efficacy of this treatment in GIST patients harboring a germline *KIT* mutation. This paper describes a 52-year old patient with a de novo germline p.Trp557Arg mutation with multiple GISTs throughout the gastrointestinal tract and cutaneous hyperpigmentation. Imatinib treatment showed long-term regression of the GISTs and evident pathological response was seen after resection.

Remarkably, the hyperpigmentation of the skin also diminished during imatinib treatment. Genetic screening of the family revealed the same mutation in two daughters, both with similar cutaneous hyperpigmentation. One daughter, aged 23, was diagnosed with multiple small intestine GISTs, which were resected. She was treated with adjuvant imatinib which prompted rapid regression of the cutaneous hyperpigmentation. Imatinib treatment in GIST patients harboring a germline *KIT* mutation shows favorable and long-term responses in both the tumor and the phenotypical hyperpigmentation.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most com-mon mesenchymal tumors in the gastrointestinal tract. Median age of diagnosis is around 60 years.(1) GIST can occur anywhere in the gastrointestinal tract, but predominantly arises in the stomach and small intestine. In 85% an activating somatic mutation in the tyrosine kinase receptor *KIT* or platelet-derived growth factor alpha (*PDGFRA*) receptor is found.(2) In locally advanced and metastatic disease, imatinib, a selective *KIT* and *PDGFRA* inhibitor, is effective for almost 90% of patients with advanced disease.(1) In addition, adjuvant imatinib in patients with local disease and high risk of recurrence can improve progression-free survival (PFS) from 36 to 65.6%.(3, 4) However, efficacy of imatinib in GIST depends on the type of gain-of-function mutation and affected codon. GISTs harboring a mutation in *KIT* exon 11 are most common and have the highest benefit of imatinib. GISTs are mostly sporadic, but can also occur in patients with genetic predisposition. Familial GISTs are mostly related to syndromes such as neurofibromatosis type 1 (NF1) or the Carney–Stratakis syndrome, associated with a succinate dehydrogenase (SDH) deficiency. Familial GISTs associated with germline *KIT* or *PDGFRA* mutations on the other hand are very rare. Thirty-five families and eight individuals, with either a de novo mutation or unknown family history, with germline mutations in *KIT* or *PDGFRA* have been reported in literature.(5–28) To our best knowledge, this is the fourth paper describing patients with germline p.Trp557Arg mutation; prior to this paper two families and one individual with GIST associated with the same germline mutation were described.(5, 20, 29) With regard to the rarity of this syndrome, the effect of imatinib in GIST patients harboring a germline *KIT* mutation has not often been described.(7, 11, 30) In some studies imatinib was withheld considering the lack of evidence for favorable responses in these patients.(10) This paper describes the effects of imatinib on the GISTs and the cutaneous hyperpigmentation associated with this syndrome in two related GIST patients. Additionally, we give an overview of literature on the effect of imatinib in GIST patients harboring a germline *KIT* mutation.

Case 1

In 1999 a then 36-year-old woman with a long history of pain in the upper abdomen and weight loss underwent gastroscopy showing multiple gastric tumors. Explorative laparotomy was performed and widespread tumor localizations in the entire gastrointestinal tract were found. Curative resection was therefore deemed not possible. Histopathological examination on samples from the stomach, small bowel and appendix revealed CD117 and CD34 positive spindle cells and no mitotic activity was found. The diagnosis multifocal low grade gastrointestinal stromal tumor (GIST) was made and a wait-and-see policy was initiated with frequent follow-up. After two years, two GIST lesions in the small bowel and the stomach showed radiological apparent progression

in size. Imatinib mesylate was then recently approved for the treatment of GIST. Initiation of imatinib 400 mg resulted in rapid tumor regression, followed by long-lasting disease stability (Figure 1). Also, pigmentations of the skin, commenced at the age of 12 on the face, hands, and feet, diminished within 3 weeks of imatinib treatment. After 7 years of imatinib treatment, resection of the three remaining lesions (gastric, small bowel, and perirectal) with curative intent was performed. Histopathological analyses of the gastric lesion revealed merely calcification and fibrosis and no viable tumor. For the other lesions the diagnosis GIST without mitotic activity was confirmed. Treatment with imatinib was well tolerated for another 5 years. Follow-up computed tomography (CT) scans showed complete remission. Twelve years after initiation, imatinib treatment was discontinued. After 1 year of discontinuation of imatinib, recurrence of a GIST in the small bowel was seen. Imatinib was restarted and after 3 months a resection of a 13 mm lesion was performed. Morphologic features were consistent with low grade GIST. It is uncertain if this was a recurrence of a previous lesion or a new primary lesion. Given the earlier response to imatinib and the occurrence of a new lesion after imatinib discontinuation, lifelong imatinib therapy was agreed on. Fifteen months after resection, no evidence of disease was found. Considering the multi-localization of the disease, the young onset, and the depigmentation under imatinib treatment, mutational analyses was performed to explore the presence of a germline mutation. Family history was unremarkable. Mutational analyses in the patient's blood showed a heterozygous c.1669 T > C, p.Trp557Arg mutation in exon 11 of the *KIT* gene. The *KIT* gene was analyzed by polymerase chain reaction (PCR) and sequencing of both DNA strands of the entire coding region and the highly conserved exon–intron splice junctions. Neither of the patient's parents showed apparent pigmentations of the skin and molecular analyses on blood samples of both parents showed absence of the defect, indicating a de novo germline *KIT* mutation. At time of diagnosis, the patient had three under-aged healthy daughters. Considering their young age and the uncertainty of the implications and prognosis of a potential positive bearer status for germline *KIT*, a decision was made not to perform genetic analyses at that time and to wait-and-see until they reach adulthood.

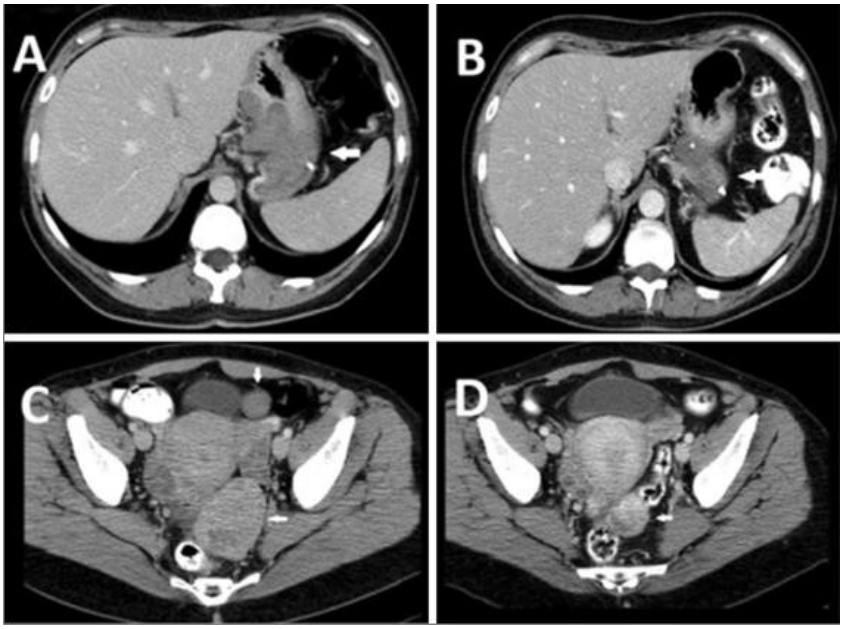

Figure 1: Both gastric lesions (A,B) and pararectal lesions (C,D) show apparent regression within 6 months after initiation of imatinib treatment.

Case 2

After reaching adulthood, the 23-year-old daughter of the patient in case 1 came to our clinic together with her two sisters, aged 22 and 19, for genetic testing. DNA sequencing analyses was conducted in two different DNA-isolations to test for the same germline *KIT* exon 11 mutation as the mother, c.1669T > C, p.Trp557Arg. Our 23-year-old patient and her 22-year-old sister tested positive (Figure 2). Both had prominent hyperpigmentation on the hands, feet, axilla, and groin, as well as friction-induced and trauma-induced pigmentation (Figure 3A). The histopathology of these pigmentations consisted of hyperpigmentation with normal melanocytes in morphology and number. Biannual screening by MRI enteroclysis was initiated and showed no tumor in the 22-year-old sibling. In our 23-year-old patient however, two adjacent small bowel lesions were found, 27 and 38 mm in diameter (Figure 4A). ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) confirmed two FDG-active lesions and no other tumor activity in the abdomen (Figure 4B). Laparoscopic resection of the involved segment of the jejunum was performed. Histopathologic analyses revealed a 42 mm and a 39 mm spindle cell type lesion and up to one mitosis per 5 mm^2, consistent with low grade GIST. In the non-tumorous part of the jejunum near the myenteric plexus a profound segmental hyperplasia of the interstitial cells of Cajal was seen (Figure 5B, C). In a multidisciplinary meeting an indication for adjuvant treatment with imatinib 400 mg for at least 3 years was

agreed on. After 3 years a possible extension of this period will be discussed. This decision was based on the expected reoccurrence of GIST given the multilocalization of GIST, the germline *KIT* mutation, and morphologic precursor changes in the non-tumorous parts of the gastrointestinal tract. Similar to the mother, her pigmentations diminished and in general the skin tone and hair color seemed lighter within 3 months of imatinib treatment (Figure 3B). Imatinib toxicity was mild, including fatigue and grade 1 muscle cramps. After 15 months of treatment, no evidence of disease was found.

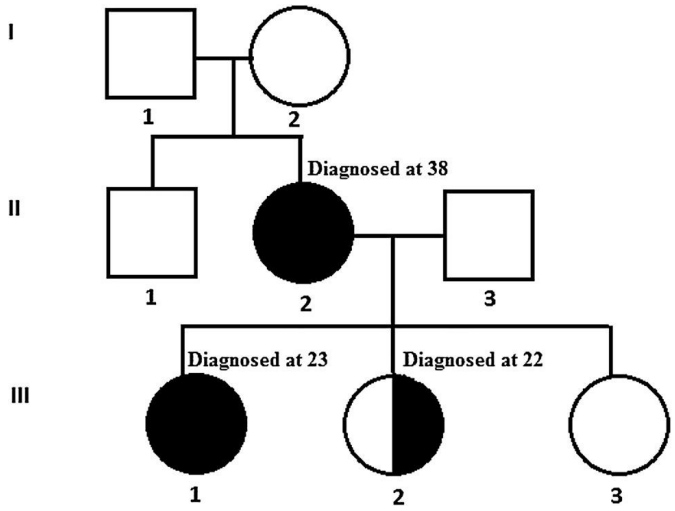

Figure 2: Pedigree of the family with age at time of diagnosis of the germline p.Trp557Arg mutation in *KIT* exon 11. Black symbols cases with mutation and GIST; black and white symbols cases with mutation but no GIST detected; squares males; circles females.

Figure 3: (A) Before initiation of imatinib mesylate there was apparent pigmentation on the hand, especially on the phalanges. (B) After 3 months of imatinib treatment the pigmentations diminished, and the overall skin tone became lighter.

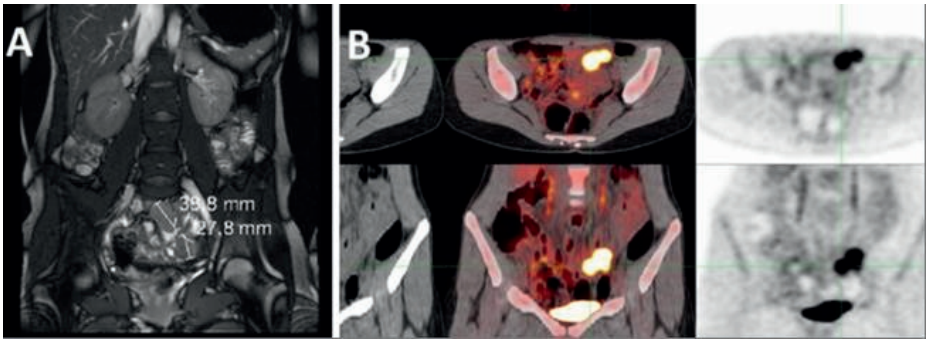

Figure 4: (A) Screening by MRI enteroclysis in our 23-year old patient showed two lesions (38 and 27 mm). (B) FDG-PET confirmed the presence of two active lesions and no other lesions were found.

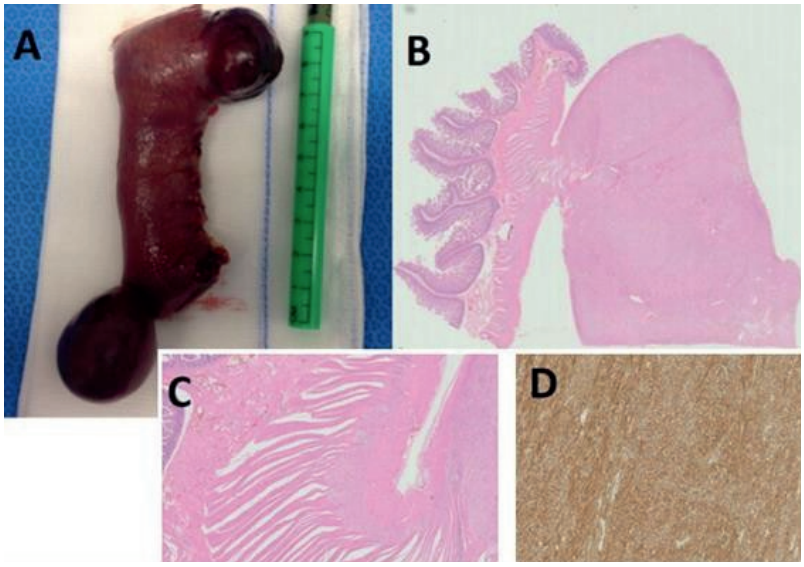

Figure 5: (A) Partial jejunum resection with the two GIST lesions in the 23-year-old patient described in case 2. (B) Hematoxylin and eosin (H&E) staining of part of the jejunum with the exophytic growing GIST (original magnification: ×20). (C) H&E stained close-up of the trajectory from the tumor to the non-tumoral part showing hyperpla-sia of the interstitial cells of Cajal (original magnification: ×40). (D) Immunohistochemical expression of DOG1 (original magnification: ×80).

Table 1: Patient characteristics.

Case	Type of mutation	Age of GIST diagnosis	Effect of imatinib on tumor	Effect of imatinib on cutaneous hyperpigmentation	Follow-up
Graham et al. [9]	*KIT* exon 13, p.Lys642Glu	56	SD	NA. Pre-existent vitiligo was unrelated	SD after 19 months
Campbell et al. [28]	*KIT* exon 11, unspecified	49	Not specified	Diminished within 3 months	2 years
Adela Avila et al. [27]	*KIT* exon 11, p. 559V > A	27, 30, 32, 35	Not specifically speci fied. 'progressive reduction of tumors'	Reduced melanosis	Unknown
Bamba et al. [5]	*KIT* exon 11, p.Val560del	43	CR and PR in most lesions	NA	1 year
Piqueres-Zubiaurre et al. [29]	*KIT* exon 11, p.Leu576Pro	Unknown (mother of 11-year old patient)	CR	Lightening of the skin	Unknown
Case 1, this paper	*KIT* exon 11, p.Trp557Arg	36	PR	Diminished within 2 weeks	NED after 13 years
Case 2, this paper	*KIT* exon 11, p.Trp557Arg	23	NA	Diminished within 3 weeks	NED after 15 months

[a] Univariate analyses using Chi-square test for categorical variables and Mann-Whitney U for continuous variables.

[b] Defined as GISTs needing neo-adjuvant imatinib treatment before surgery is deemed possible or safe.

Discussion

GISTs are mostly sporadic and GISTs associated with germline *KIT* mutations are very rare. Up until today 35 families and 8 individual patients have been described before, with various phenotypical characteristics. Patients were described to have pigmentation anomalies, urticarial pigmentosa, dysphagia, and/or mastocytosis. This paper describes the occurrence of GIST and hyperpigmentation in a family with a mother with de novo germline p.Trp557Arg mutation in the *KIT* exon 11 gene. We show a remarkable and long term effect of imatinib in the GISTs. In addition, in both cases there was a striking effect on the pigmentation anomalies of the skin. Within weeks of imatinib treatment these pigmentations diminished and it even seemed like the overall skin tone became lighter. This effect of imatinib in the skin is described three times before in a GIST patient with a germline *KIT* mutation (Table 1).(30–32) C-KIT and its ligand stem cell factor (SCF) are believed to regulate the development and survival of melanocytes. By introduction of a tyrosine kinase inhibitor such as imatinib, the function of c-KIT is altered and may be responsible for impaired pigment production.(31) In general, GISTs with a somatic mutation in exon 11 of the *KIT* gene are previously known to have exceptionally good responses in sporadic GISTs with a partial response rate of almost 84%.(33) This is the

sixth paper describing the in vivo effect of imatinib in patients with GIST associated with a germline mutation in *KIT* exon 11 (Table 1). Similar results have been described in a prior study with an elderly patient receiving half-dose of imatinib (200 mg/ day).(7) In vitro, one other study described good responses to imatinib and nolitinib in a GIST associated with a germline *KIT* exon 11 mutation.(34) In this patient an expectant policy was chosen rather than a tyrosine kinase inhibitor. Another study has described the effect of imatinib in a patient with multilocalized GIST associated with a germline *KIT* exon 13 mutation (11) (Table 1). After imatinib treatment some lesions showed regression while others showed stable disease. He had ongoing response after 19 months.

Prolonged imatinib treatment might be debatable, since GISTs harboring a somatic p.Trp557Arg substitution are known to have a relatively indolent behavior.(4) However, a prior study on a large kindred with p.Trp557Arg germline mutation described several family members requiring prolonged hospitalization and three members have died most probably as a result of disease progression.(20) In another case with this type of germline mutation a 52-year old patient died eventually of disease progression. At that time, no imatinib was available yet.(16)

In this paper, two out of three daughters harbored a germline *KIT* mutation and had, other than pigmentations, no symptoms. This is the first paper describing GISTs associated with a germline *KIT* mutation detected by screening. In line with earlier recommendations, we conducted MRI in both daughters, resulting in surgery and systemic treatment in one daughter.(6) It is unclear what the consequences of a wait-and-see approach would have been. In a similar study on a family with germline *KIT* exon 11 mutation imatinib was withheld given the lack of evidence for symptom reduction and prolonged survival in these patients.(10) However, considering the symptomatic and progressive behavior of the GISTs in the mother and the cases described in prior literature, we could not assume an indolent course. Therefore, regular screening and, in case of presence of disease, treatment with imatinib was agreed on. The other sibling with a germline *KIT* mutation was not treated with imatinib given the lack of evidence for efficacy of imatinib for prevention of GIST.

In conclusion, GISTs associated with germline *KIT* mutations are very rare. Up until today, little to no evidence for long-term introduction of imatinib has been provided. We showed that imatinib treatment in GIST patients harboring a germline *KIT* exon 11 mutation does induce favorable and long-term responses in both the tumor and the phenotypical hyperpigmentation associated with this syndrome. Imatinib treatment should therefore be considered in these patients.

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